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Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria

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Abstract

Individuals who experience a gender identity that is discordant with biological sex are increasingly presenting to physicians for assistance in alleviating associated psychological distress. In contrast to prior efforts to identify and primarily address underlying psychiatric contributors to gender dysphoria, interventions that include uncritical social affirmation, use of gonadotropin-releasing hormone agonists to suppress normally timed puberty, and administration of cross-sex steroid hormones to induce desired secondary sex characteristics are now advocated by an emerging cohort of transgender medicine specialists. For patients with persistent gender dysphoria, surgery is offered to alter the appearance of breasts and genital organs. Efforts to address ethical concerns regarding this contentious treatment paradigm are dependent upon reliable evidence on immediate and long-term risks and benefits. Although strong recommendations have been made for invasive and potentially irreversible interventions, high-quality scientific data on the effects of this approach are generally lacking. Limitations of the existing transgender literature include general lack of randomized prospective trial design, small sample size, recruitment bias, short study duration, high subject dropout rates, and reliance on "expert" opinion. Existing data reveal significant intervention-associated morbidity and raise serious concern that the primary goal of suicide prevention is not achieved. In addition to substantial moral questions, adherence to established principles of evidence-based medicine necessitates a high degree of caution in accepting gender-affirming medical interventions as a preferred treatment approach. Continued consideration and rigorous investigation of alternate approaches to alleviating suffering in people with gender dysphoria are warranted.

Summary: This paper provides an overview of what is currently known about people who experience a gender identity that differs from their biological sex and the associated desire to engage the medical profession in alleviating associated discomfort and distress. The scientific evidence used to support current recommendations for affirming one's preferred gender, halting normally timed puberty, administering cross-sex hormones, and surgically altering primary and secondary sexual traits are summarized and critically evaluated. Serious deficits in understanding the cause of this condition, the reasons for the marked increase in people presenting for medical care, together with immediate and long-term risks relative to benefit of medical intervention are exposed.

Keywords

Cross-sex hormones, Evidence-based medicine, Gender dysphoria, Gender identity, Medical research, Puberty blockade, Risk–benefit analysis, Sexuality, Suicide, Transgender operations

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Patients who experience a gender identity that is discordant with biological sex have an alarmingly high incidence of serious psychosocial morbidity including depression, anxiety, eating disorders, substance abuse, HIV infection, and homelessness (Connolly et al. 2016). Most concerning, nearly half of all affected individuals will contemplate suicide and a third will attempt suicide (Adams, Hitomi, and Moody 2017). While a need for effective treatment modalities is clear, there are significant deficiencies in understanding the etiology of this condition, the risks and benefits of proposed medical interventions, and the long-term success of various approaches in achieving the primary desired goal of preventing suicide (Institute of Medicine 2011; Olson-Kennedy et al. 2016). With a desire to provide real and sustained assistance to patients who experience gender dysphoria within established ethical boundaries, it is essential to understand the scientific evidence used to support proposed medical interventions and acknowledge the limits of these data.

To adequately address the role of healthcare providers in treating patients with gender dysphoria, it is necessary to define this clinical condition in a way consistent with established scientific understanding of sex as a biological trait intrinsically ordered to the purpose of procreation. Despite ideologically influenced efforts to portray sex along a continuum, reproductive biology is inherently binary. Specifically, there are only two gonads (testes and ovaries) that contribute to the conception of new human life. The existence of individuals with disorders of sexual development (DSDs) does not alter this basic biological reality (Eid and Biason-Lauber 2016). In many individuals with DSDs, fertility is absent or severely impaired (Lee et al. 2006, 2016). When genital ambiguity is present, there are established clinical pathways involving hormonal, genetic, and imaging studies to assist clinicians in determining the sex of the affected child (Lee et al. 2016). In these rare cases, which affect <0.02 percent of all infants, the physician must make a tentative sex assignment at the time of birth. For the remaining 99.9% of infants, sex is not "assigned" at birth but rather is correctly recognized by the observation of the appearance of the external genitalia. Nearly all patients who present to medical establishments for the treatment of gender dysphoria have normally formed and functioning sexual anatomy and function prior to hormonal or surgical intervention.

Although the ability to obtain accurate information on the number of people who experience a gender identity that is discordant with biological sex has remained challenging, several sources have reported a marked increase in the number of patients presenting to specialized clinics that offer gender affirmation services. In the Fifth Edition of the *Diagnostic and Statistical Manual* (DSM-5) used to classify psychiatric disease, the reported prevalence of "gender dysphoria" was 0.005 percent to 0.014 percent for adult males and 0.002 percent to 0.003 percent for adult females (American Psychiatric Association [APA] 2013). Epidemiologic data from Sweden have demonstrated rising prevalence of individuals claiming a transgendered identity who sought treatment over the past fifty years, with most of the increase since 2000 (Dhejne et al. 2014). Some more recent estimates have suggested a prevalence as high as .4 percent of the US population (Meerwijk and Sevelius 2017).

Assessing the accuracy of these estimates requires consideration of the methodologies used. Higher estimates rely upon patient responses to questionnaires in which answers appear to be influenced by the wording of the questions asked. There is evidence that male to female ratio of individuals with sex–gender identity discordance has reversed, with more recent estimates showing that much of the observed increase is due to biological females who identify as male (Zucker 2017). It is frequently claimed, without documented scientific evidence, that this increase is driven by an increase in existing patients coming forward for treatment rather than a change in overall incidence or change in rates of persistence among affected youth. The degree to which social affirmation of transgendered identity has affected these epidemiologic trends is unknown. Recently, the phenomenon of adolescent girls with no prior expression of gender dysphoria presenting as having a transgendered identity in social networks has been reported (aka rapid onset gender dysphoria; Littman 2018). This study is limited by relatively small sample size and a significant risk of ascertainment bias. Further research is required to establish the validity and extent of this phenomenon.

Understanding of the cause of any medical condition greatly assists efforts to develop effective treatment strategies. To date, the cause of discordance between sex and gender identity remains unknown. There is no available blood test or imaging procedure that can be used to determine a person's self-perceived gender identity. Evaluation relies exclusively in the domain of patient report of internally held feelings and beliefs. There are, however, published data that provide potential clues to influencing factors (Saleem and Rizvi 2017). This includes several reports of structural and functional differences between brains of individuals with sex-

discordant gender identity compared to brains from people with gender identity that matches sex (Burke et al. 2014; Luders et al. 2009; Kruijver et al. 2000). Among the limitations of these data are significant overlap between male and female brain structures and heterogeneity between individuals. This precludes the ability to determine sex by examining structure alone. Furthermore, the existing data on brain structure and function do not account for the known phenomenon of neuronal plasticity (i.e., environmental stimuli can alter brain structure; Ismail, Fatemi, and Johnston 2017). Thus, it is not clear whether changes in brain structure are the cause or effect of transgendered identity and behavior.

It is known that prenatal and perinatal hormone exposure can alter sexual phenotype (i.e., the physical appearance of the body; Jost et al. 1973). The degree to which these hormones influence gender identity remains an area of active investigation (Berenbaum and Beltz 2016). Although insight has been gained by study of DSDs, there is conflicting evidence on the nature and magnitude of this effect and the dependence upon the etiology of the developmental defect. For example, female infants born with congenital adrenal hyperplasia (CAH), a condition that exposes the developing baby to high levels of male hormones (androgens), often exhibit typical male preferences and behaviors. Several potential explanations for this phenomenon that are independent of prenatal male hormone exposure have been proposed (Jordan-Young 2012). Importantly, the vast majority of affected children with CAH historically did not experience self-perceived transgender identity or gender dysphoria (Zucker et al. 1996).

Limited data also suggest a role of genetics in gender identity. This includes investigation of identical twins (Heylens et al. 2012). Because identical twins have exactly the same genes, if gender identity is exclusively determined by genetics, one would predict that there would be 100 percent concordance in identical twin pairs (i.e., if one twin experienced transgender identity, the other twin would also share this experience). However, the observed concordance is closer to 40 percent of affected twins. There are ongoing efforts to sequence the genomes of individuals with sex-discordant gender identity to find a specific gene (or genes) that contribute(s) to this experience (Yang et al. 2017). The data published to date addressing this question provide potential clues, but similar to the limitations of with brain structures, there is considerable overlap between affected and nonaffected individuals (Foreman et al. 2019). Thus, it is likely that influences, whether primary or secondary, are polygenetic (i.e., the genetic differences are many, with each contributing only a small fraction of the observed phenotype).

The presence of genetic differences does not mean that the genetic variation is the cause of an individual's identity. There are numerous alternate hypotheses that can be proposed (e.g., a genetic difference in resiliency). Several reports have found high co-occurrence of autism in children with gender dysphoria (Glidden et al. 2016). Thus, in light of existing data, it can be reasonably concluded that the cause of gender dysphoria is multifactorial with both genetic and environmental contributions. Further research is needed to establish the number of contributing factors and to determine relative influences for individual patients. Heterogeneity among patient populations is likely to complicate efforts to make generalizable outcome predictions in clinical studies, particularly with small randomized trial designs.

In children who express gender discordance, the majority will experience reintegration of gender identity with biological sex by the time of puberty in the absence of directed medical or societal intervention. This is supported by nearly a dozen published studies over the past forty years. Many of the earlier studies included a small number of subjects and used definitions of gender discordance (e.g., gender identity disorder) that differ from current criteria for gender dysphoria as listed in the *DSM-V* (APA 2013). In some studies, loss of patients to follow-up hinders determination of desistance (Wallien and Cohen-Kettenis 2008). The most recent studies report desistance rates near 85 percent (Steensma et al. 2011; Drummond et al. 2008).

There is some evidence that the degree of distress experienced by a gender dysphoric child correlates with the likelihood of spontaneous resolution (Steensma et al. 2013). Whether and to what extent changes in social and medical approaches to dealing with individuals with transgender identity alters the rate of desistance is unclear, but there is indirect evidence that such effects may occur (de Vries et al. 2011). For patients who experience sex-discordant gender identity beyond puberty, there are relatively few published reports of desistance. Most of these data are found among case reports and personal testimony outside of peer-reviewed journals (Heyer 2018; Meijer et al. 2017). There are several hypotheses that can be put forth to account for this observation including differences between children and adults with respect to underlying etiology and the effects of extended social reinforcement. As in affected children, there are few data on the influence of gender-affirming medical procedures on altering desistance rates.

Before addressing specific aspects of medical interventions intended to alleviate gender dysphoria, several general observations can be made regarding the published literature in this field. Despite the endorsement of gender affirmation approaches by several medical organizations including the Endocrine Society (Hembree et al. 2017) and the World Professional Alliance for Transgender Health (WPATH; Coleman et al. 2012), it is important to recognize the low quality of scientific evidence used in generating these treatment recommendations. With the publication of both the initial treatment guidelines by the Endocrine Society guidelines in 2009 and revised guidelines in 2017, the Grading of Recommendations, Assessment, Development and Evaluations system was used to assess data quality (Guyatt et al. 2008). This system ranks evidence into four categories (strong, moderate, low, and very low). Nearly all of the recommendations made were based upon "low" or "very low" quality evidence. By definition, these designations mean that there is a high likelihood that the attainment of new data will necessitate changes to the guidelines provided. The only data that reached the level of "moderate" quality were related to adverse medical outcomes. The limitations of the published studies in the growing field of transgender medicine are many. They include a general lack of randomized controlled trial design, small sample sizes, high potential for recruitment bias, questions regarding the precision of measured parameters, nongeneralizable population groups, relatively short follow-up, high numbers of patients lost to follow-up, and frequent reliance upon "expert opinion" alone. While such deficiencies are not unique to this field of investigation, the strength of the recommendations made on the basis of this type of evidence is, in many respects, disproportionate. In other areas of medicine, much greater caution is generally applied to advancing a single treatment approach over other potential interventions.

The care of patients who experience gender dysphoria has included efforts to understand and address underlying psychosocial morbidity (Brown and Jones 2016; de Graaf et al. 2018; Kaltiala-Heino et al. 2015). Underlying factors that have been investigated include unresolved developmental challenges, underlying depression and anxiety disorders, strained family relationships, sexual abuse, autism, and peer conflicts (Saleem and Rizvi 2017). The pioneering work of Zucker established that many but not all patients who received psychological counseling and support were able to manage and resolve conflicts arising from discordant gender identity, particularly in affected children (Zucker et al. 2012).

Among contemporary approaches to alleviate gender dysphoria are efforts to support and encourage affected patients to adopt a social role in accord with gender identity irrespective of biological sex. Social transition includes the use of preferred name and pronouns, cross-dressing, and access to sex-segregated facilities corresponding to perceived gender identity. Since the widespread adoption of interventional strategies directed toward affirming transgender identity, efforts to identify psychological approaches to mitigate dysphoria, with or without desistance as a desired goal, have largely been abandoned. The WPATH has rejected psychological counseling as a viable means to address sex–gender discordance with the claim that this approach has been proven to be unsuccessful and is harmful (Coleman et al. 2012). Yet the evidence cited to support this assertion, mostly from case reports published over forty years ago, includes data showing patients who benefited from this approach (Cohen-Kettenis and Kuiper 1984). Although largely unstudied, cognitive behavioral therapy in particular may have significant benefit to this patient population by reducing social anxiety (Busa, Janssen, and Lakshman 2018). To date, there have been no randomized controlled trials investigating the risks and benefits of social transition.

There have been studies that report positive effects of nonmedical interventions: cross-sectional data on preferred name use have reported significant short-term improvement in self-reported sense of well-being (Russell et al. 2018). Furthermore, children who have undergone social transition with parental support have reported reduced levels of dysphoria (Durwood, McLaughlin, and Olson 2017; Olson et al. 2016). Limitations of these data include small sample size, restriction of study subjects to those with mild dysfunction, reliance on parental report, and lack of long-term follow-up.

A variety of medical interventions have been introduced to support physical changes in the appearance and function of primary and secondary sexual organs to align with an individual's desired gender role when this is discordant with biological sex. This includes hormonal blockade of normal pubertal development in adolescent children, administration of cross-sex hormones (i.e., testosterone to females desiring to appear male and estrogen to males desiring to appear female), and surgery to alter the appearance of primary and secondary sexual features. While surgical procedures have been available to affected adults for decades, the use of such

interventions in children has only recently been advocated (de Vries and Cohen-Kettenis 2012).

Long-acting gonadotropin-releasing hormone (GnRH) agonists (aka "puberty blockers") have been recommended to halt pubertal progression when this process occurs prematurely in children (Carel et al. 2009). Purported justification of this intervention for children with persisting dysphoria includes overall safety of these medications, allowance of more time for a child to explore their gender identity, reversibility upon treatment cessation for desisting individuals, and prevention of irreversible changes in secondary sexual characteristics for patients with persistent gender discordance. Yet the use of this intervention remains controversial (Vrouenraets et al. 2015; Giovanardi 2017). There are a few relatively small studies that have demonstrated improved sense of well-being and reduced dysphoria in adolescent transgendered youth who receive puberty-blocking drugs (de Vries et al. 2011, 2014), but there are also significant concerns related to associated risks (Hruz, Mayer, and McHugh 2017). First, there are limited data specifically assessing the long-term safety of delaying normally timed puberty (Schagen et al. 2016). This class of medication has not been approved by the US Food and Drug Administration for use in halting normally timed puberty for gender-dysphoric youth (AbbVie 2018). Risks include osteopenia (low bone density), altered adult height, and impaired special memory (de Vries et al. 2011; Hough et al. 2017). Rather than merely providing more time for the exploration of gender identity, there is a concern that most if not all children exposed to this intervention will proceed to cross-sex hormone therapy (de Vries et al. 2011). While cessation of GnRH agonist administration will allow resumption of the signals that direct gonadal maturation, the interruption of a normal developmental process, which is time-dependent, cannot be "reversed."

In the peer-reviewed literature on individuals who have undergone gender-affirming medical procedures to change bodily appearance, relatively low rates of regret and desire to "de-transition" to a gender role corresponding to biological sex have been observed (Wiepjes et al. 2018). Due to limitations in available data, questions remain regarding long-term satisfaction, particularly when initiated in adolescent children (Mahfouda et al. 2019). Most reports are from retrospective chart review or longitudinal study design.

None of the available studies include matched randomized prospective control groups. There is a deficiency of scientific study systematically assessing this patient population to understand factors that are correlated with and may contribute to failure to achieve lasting relief of dysphoria following the affirmation of discordant gender identity. Affected individuals who desire to transition back to a gender role concordant with biological sex have reported negative social stigma similar to or in some cases exceeding that encountered prior to their initial medical intervention to support transgendered identity (Heyer 2018).

The available data on the long-term effects of gender affirmation in this patient population indicate that the most serious concern, suicide, remains significantly elevated above the background population after medical intervention to alter sexual appearance. Specifically, a thirty-year follow-up study in Sweden on patients who had undergone medical transition showed a rate of completed suicide that was nineteenfold above the backgrounds population (Dhejne et al. 2011). Because this was not a controlled study, it is not possible to assess the impact of the medical treatments themselves on outcomes. However, these data clearly show that this approach did not resolve the problem of depression and suicide.

Further indicating a lack of efficacy of this approach is a recent meta-analysis in North American patients, where suicidal ideation was assessed over the course of an individual's lifetime and within the past year (Adams, Hitomi, and Moody 2017). In this report, suicide rates were similar in both groups. The few studies that examined suicidal ideation before and after gender transition found suicidal ideation to be increased.

In addition to remaining questions regarding the efficacy of hormonal and surgical efforts to align the body of an individual with gender dysphoria to his or her desired sex, the safety of these interventions is only partially understood, particularly when administered to children. A known consequence of cross-sex hormone administration is the disruption of gonadal function and the signals that regulate human reproduction. The infertility that results can be irreversible, particularly where this intervention is undertaken prior to full gonadal maturation (Hembree et al. 2017). Androgen levels achieved in female patients given testosterone exceed those observed in women with polycystic ovarian syndrome and frequently reach levels seen in androgen-secreting tumors with associated cardiovascular risk (Macut, Antić, and Bjekić-Macut 2015). Males receiving estrogen have a fivefold increase in the incidence of thromboembolic stroke (Getahun et al. 2018). Adverse metabolic effects that increase the risk of cardiovascular disease have also been reported (Irwig 2018; Maraka et al. 2017). The

influence of cross-sex hormones on cancer risk remains unclear. Potential risks for cancer development include exposure to cross-sex hormones, effects of sexually transmitted diseases (i.e., some sexually transmitted diseases increase risk of some cancers), and failure to obtain recommended screening in patients presenting to medical facilities with a gender that does not match biological sex. Further research is needed to adequately address this serious concern (Braun et al. 2017).

In summary, the information presented in this report highlights many of the deficiencies in the existing knowledge base regarding the etiology and prevalence of gender dysphoria and current treatment approaches. Although far from exhaustive, these data provide a rationale for exercising caution in accepting the currently proposed gender affirmation treatment paradigms that have been advocated by the WPATH (Coleman et al. 2012) and other professional organizations (Hembree et al. 2017). With heightened awareness of the suffering experienced by individuals who experience a gender identity that is discordant with biological sex, there remains a strong moral imperative to engage this vulnerable patient population. As increasing numbers of affected people, both children and adults, are presenting to medical centers for help, there is a need to better understand this condition and provide means to address all associated medical needs. This includes efforts to welcome and support individuals claiming a transgendered identity with the provision of routine medical care and treatment (Rahman, Li, and Moskowitz 2019). As in all other areas of medicine, efforts to provide safe and effective clinical care of patients with gender dysphoria should be grounded on sound scientific evidence. Where this evidence is lacking, academic healthcare institutions have an opportunity to contribute to rigorous clinical investigation of novel treatment approaches. This can include efforts to better understand psychological influences on gender identity and the design of properly controlled clinical trials using modern psychiatric approaches such as cognitive behavioral therapy (Butler et al. 2006). Administrators who are charged with developing institutional policy and educating staff on the complexity of this unique condition and diverse patient population can benefit from recognizing the ambiguities present. Physicians who deliver this care can also remain mindful of the long history of the harms that have been done to patients from the use of unproven medical interventions (Johnson 2014). Ongoing critical appraisal of emerging scientific evidence and continued open dialogue regarding potential alternate approaches to the care of individuals with sex–gender discordance provides hope for lasting benefit, both to affected patients and to society as a whole.

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